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(72) Inventors TSUNG-YING SHEN, GORDON LYN WALFORD, BRUCE EDWARD WITZEL and HOWARD JONES

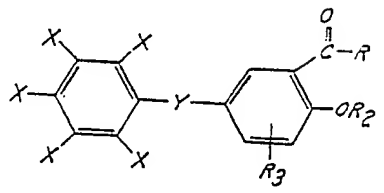
(54) SUBSTITUTED SALICYLIC ACID COMPOUNDS

(71) We, MERCK & CO. INC., a corporation duly organised and existing under the laws of the State of New Jersey, United States of America, of Rahway, New Jersey, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement: —

The development of anti-inflammatory compounds in the past two decades has involved the appearance of a great many new drugs. Many of these have been steroids of 11 - oxygenated pregnane series. These, while highly effective, have the drawback of causing many side effects. There is a need in the market for equally effective compounds of much simpler structure and having fewer side effects.

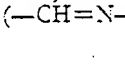
This invention is concerned with substituted salicylic acid compounds, processes for producing them, and pharmaceutical compositions containing such compounds as an active ingredient.

The compounds of the present invention have the following general formula:



in which R is a hydroxy, amino, alkoxy, alkylamino, dialkylamino, dialkylaminoalkylamino, dialkylaminoalkoxy, hydroxyalkoxy, poly - hydroxyalkoxy, alkoxyalkoxy, phenylalkoxy, phenoxy, substituted phenoxy, (C_{1-6} alkanoylamino)alkoxy, hydrazino, anilino, morpholino, N - piperidino, pyrrolidino or hydroxyalkyl - amino radical or an N - attached radical derived from an amino acid; R_2 is a hydrogen atom or an acyl, alkyl or alkoxycarbonyl radical; R_3 is a hydrogen or halogen atom or a haloalkyl, alkyl, cycloalkyl or alkoxy radical; each X, which may be the same as or different from the others, it is hydrogen or halogen atom or an alkyl, hydroxy, alkoxy, acyloxy, haloalkyl, nitro, amino, alkylamino, dialkylamino, acylamino, mercapto, alkylthio, alkylsulfinyl, alkylsulfonyl, sulfamoyl, aminosulfinyl, aminoalkyl, alkylaminoalkyl, dialkyl -

aminoalkyl, hydroxyalkyl, alkoxyalkyl, mercaptoalkyl, alkylthioalkyl, cyano, carboxy, alkoxycarbonyl, carbamoyl, aryl, aralkyl, salicyl, aryloxy, or aralkoxy radical; and Y is a methyleneimino ($-CH_2-NH-$), iminomethylene ($-NHCH_2-$), methinenitrilo ($-CH=N-$), nitrilomethine ($-N=CH-$)



or carbonylimino ($-CNH-$) radical, all alkyl and alkoxy radicals and residues mentioned in the definitions of R, R_2, R_3 and X containing not more than five carbon atoms unless forming part of an alkoxycarbonyl radical.

In a preferred group of compounds of the present invention R is a hydroxy or amino radical; R_2 is a hydrogen atom or an alkyl radical; R_3 is a hydrogen or halogen atom or an alkyl radical; and X is a hydrogen or halogen atom or an alkoxy, haloalkyl or dialkylamino radical.

Possible values of R include methoxy, ethoxy, butoxy, pentoxy, methylamino, propylamino, pentylamino, dimethylamino, dibutylamino, propylpentylamino, 3 - hydroxypropoxy, 2 - hydroxypropoxy, 4 - hydroxybutoxy, 2,3 - dihydroxypropoxy, 2,3,4,5,6 - pentahydroxyhexyloxy, ethoxyethoxy, benzyloxy, phenethoxy, alkoxyphenoxy, halophenoxy, dialkylaminophenoxy, (C_{1-5} alkanoyl) - aminophenoxy, carboxyphenoxy and (C_{2-5} alkoxycarbonylphenoxy); possible values of R_2 include formyl, acetyl, propionyl, butyryl, methyl, ethyl, propyl, isopropyl, butyl, pentyl, methoxycarbonyl, ethoxycarbonyl and hexoxycarbonyl; possible values of R_3 include trifluoromethyl, methyl, ethyl, propyl, isopropyl, butyl, pentyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, methoxy, ethoxy, isopropoxy and butoxy; possible values of X include methyl, ethyl, propyl, isopropyl, butyl, pentyl, methoxy, isopropoxy, butoxy, benzoyloxy, acetoxy propionoxy, trifluoromethyl, methylamino, propylamino, pentylamino, dimethylamino, dibutylamino, propylpentylamino, formamido, acetamido, propionamido, butyramido, methylthio, ethylthio, methylsulfinyl, ethylsulfinyl, butylsulfinyl, methylsulfonyl, ethylsulfonyl, butylsulfonyl, methylaminomethyl, ethylaminomethyl, dimethylaminomethyl, diethylamino - ethyl, hydroxymethyl, hydroxyethyl, hydroxypropyl, methoxymethyl, methoxyethyl, ethoxyethyl, ethoxypropyl, mercaptomethyl, mercaptoethyl, methylthiomethyl, ethylthioethyl, ethylthiopropyl, methoxycarbonyl, ethoxycarbonyl, phenyl, halophenyl, tolyl, benzyl and phenethyl.

When R_3 is a halogen, it is preferably fluorine or chlorine, though it may also be bromine or iodine. The same applies to X.

Representative compounds of this invention are:

5 - (*p*, *o* or *m* - fluorobenzylideneamino) - salicylic acid

5 - (*p*, *o* or *m* - fluorobenzylamino) - salicylic acid

5 - (*p*, *o* or *m* - fluorobenzamido)salicylic acid

5 - (*p*, *o* or *m* - fluoroanilinomethyl) - salicylic acid

5 - (*p*, *o* or *m* - fluorophenyliminomethyl) - salicylic acid; and

the corresponding salts, esters, anhydrides and amides.

This invention also provides a method of treating inflammation in non-human animals by administering to the animals a compound of Formula I.

The compounds of the invention can be used to treat inflammation in humans as well as other animals by reducing inflammation and relieving pain in such diseases as rheumatoid arthritis, osteoarthritis, gout, infectious arthritis, and rheumatic fever. It has been found that compounds of the invention have better potency at the same dosage levels than similar types of compounds already known and that they exhibit a lower incidence of side effects.

Some compounds of Formula I also have anti-pyretic, analgesic, diuretic, anti-fibrinolytic and hypo - glycemic activity and would be administered and used in the same manner and in the same dosage ranges as if they were being used to treat inflammation as discussed further on.

The compounds may be administered orally, rectally, topically or parenterally, and the present invention provides a pharmaceutical composition comprising at least one compound of Formula I in a non-toxic pharmaceutically acceptable diluent, carrier or coating.

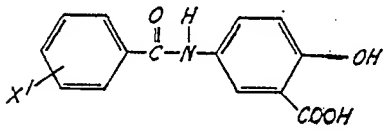
The carrier may be either a solid or a liquid. Examples of solid carriers are lactose, corn starch, gelatin, talc, sterotix, stearic acid, magnesium stearate, terra alba, sucrose, agar, pectin, cab - o - sil and acacia. Examples of liquid carriers are peanut oil, olive oil, sesame oil and water. Similarly, the carrier or diluent may include a time-delay material such as glyceryl monostearate or glyceryl distearate alone or with a wax.

Several pharmaceutical forms of the therapeutically useful compositions can be used. For example, if a solid carrier is used, the compositions may take the form of tablets, capsules, powders, pills, troches or lozenges, prepared by standard pharmaceutical techniques. If a liquid carrier is used, the preparation may be in the form of a soft gelatin capsule, a syrup, an elixir or a liquid suspension. Suppositories for rectal administration, gels, lotions, creams and ointments for topical application, and buffered injectable solu-

tions may be prepared in a conventional manner.

The active compounds are administered in an amount sufficient to reduce inflammation. Advantageously, the composition will contain the active ingredient, namely, the compounds of Formula I in an amount such that from 1 mg to 100 mg per kg body weight per day (50 mg to 7 g per patient per day), preferably from 2 mg to 50 mg per kg body weight per day (100 mg to 3 g per patient per day), and especially from 4 mg to 20 mg per kg body weight per day, can be administered. The latter amount, particularly when administered orally, has been found in general to result in the most rapid and effective anti-inflammatory action. It should be understood, however, that although preferred dosage ranges are given, the dose level for any particular patient depends upon the activity of the specific compound and that many other factors that modify the actions of drugs must be taken into account, for example, age, body weight, sex, diet, time of administration, route of administration, rate of excretion drug combination, reaction sensitivities and severity of the particular disease.

Compounds of the formula:



in which X' is a halogen atom have been found particularly effective. Such compounds can be prepared by hydrolysis of their alkyl esters.

The benzylidenenitrilo salicylic acids of this invention (i.e. those in which Y is methinenitrilo) may be prepared by reacting an aminosalicylic acid with a benzaldehyde. These compounds may be reduced to form the corresponding benzylaminosalicylic acid compounds of this invention. The benzylaminosalicylic acid compounds may also be prepared by direct benzylation of sodium (or potassium) 5 - aminosalicylate in ethanol containing anhydrous potassium carbonate.

The anilinomethylsalicylic acid compounds of this invention may be prepared by reacting a halo - methyl - salicylic acid or a methyl ester thereof with an aniline, followed by hydrolysis when the methyl ester is used.

The benzamidosalicylic acid compounds of this invention may be prepared by direct benzoylation of an amino - salicylic acid or by reducing a 4 - nitro - anisole to form a 4 - amino - anisole, reacting the amino - anisole with a benzoyl halide to form a benzamidoanisole, demethylating said benzamidoanisole to form a benzamidophenol and carboxylating said benzamidophenol.

The phenylnitrilomethinesalicylic acid compounds of this invention may be produced by reacting a 5 - formyl salicylic acid with an aniline.

It is to be understood that in the reactions mentioned above each compound may be substituted in the ring to give desired values of R, and X in the product.

The esters of this invention, e.g. compounds in which R is alkoxy, are prepared by any esterification procedure using an esterifying agent containing the appropriate R group. For example, the acid compounds of this invention may be reacted with the appropriate alkanol (preferably methanol, at elevated temperatures in the presence of a strong acid, such as hydrochloric acid, sulfuric acid or p-toluenesulfonic acid, to form the desired ester.

The amides of this invention e.g. those in which R is amino, may be prepared by any suitable amidation reaction. For example, the acid compound (preferably the methyl or ethyl ester) may be reacted with ammonia, ammonium hydroxide or an amide compound, at any suitable temperature (room temperature to reflux). When the amino group is desired, it is preferred to carry out the reaction with ammonia in a bomb at temperatures about 100°C. Preferably, when an amide is desired which is derived from an amino acid, the following reaction sequence is followed: The benzoic acid final compound is reacted with isobutyl chlorocarbonate to form the mixed anhydride. This compound is in turn reacted with the desired amino acid ester and subsequently hydrolysed to form the desired amide.

The compounds in which R_2 is alkyl (preferably methyl) may be prepared by any appropriate alkylation reaction. For example, the corresponding hydroxy benzoic acid, ester, or amide (preferably the ester), may be reacted with a dialkyl sulfate (preferably dimethyl sulfate) in the presence of a base (such as an alkali metal carbonate) at any suitable temperature (room temperature to reflux but preferably at or near reflux) with subsequent acidification of the reaction mixture, such as with hydrochloric acid or sulfuric acid.

The salts of the final acid compounds of this invention may be prepared by any of the well known metathesis procedures. For example, the acid compound may be reacted with an inorganic base, such as sodium hydroxide. The anhydrides of this invention may be prepared by any of the well known procedures.

The following examples, in which "m" means "mole", are presented to further illustrate the invention:

EXAMPLE 1

5 - (*p* - fluorobenzoylamino) - salicylic acid

To methyl 5 - aminosalicylate (0.01 m.) in pyridine at 10°C. is added *p* - fluoro - benzoyl chloride (0.01 ml), stirrings, over 10 minutes. The resulting mixture is allowed to warm to room temperature and stirred overnight. Then it is added to an excess of dilute hydrochloric acid with stirring, and the methyl 5 - (*p* - fluorobenzoylamidosalicylate collected and hydrolysed under standard conditions to yield 5 - (*p* - fluorobenzoylamino) - salicylic acid, m.p. 280—281°C.

When other substituted benzoyl chlorides, e.g. with *o* - fluoro, *m* - fluoro, *o*-, *m*-, and *p* - chloro, *o*-, *m*-, and *p* - methoxy, *o*-, *m*-, and *p* - trifluoromethyl, *o*-, *m*-, and *p* - nitro, *o*, *m*- and *p* - dimethylamino (or hydrochlorides), *o*-, *m*, and *p* - acetamido, *o*-, *m*-, and *p* - methylmercapto, *o*-, *m*- and *p* - carbomethoxy, *o*-, *m*- and *p* - phenyl, o-, *m*-, and *p* - benzyl, *o*-, *m*- and *p* - phenoxy, *o*-, *m*- and *p* - benzyloxy or *o*-, *m*- and *p* - acetyl benzoyl chloride are used, the corresponding substituted 5 - benzamidosalicylate is obtained.

When the 3 - chloro, 3 - methoxy, 3 - methyl, and 4 - fluoro analogues of methyl 5 - aminosalicylate are used in the above example in place of methyl 5 - aminosalicylate, the corresponding substituted salicylates are obtained.

The above benzoylations may be carried out by other means, such as addition of the benzoyl halide to an aqueous nitrogen-covered solution of a metal salt, such as the sodium or potassium salt, of the salicylic acid with concomitant addition of base to maintain the pH of the reaction mixture at 8. Only those benzoyl halides with groups compatible with aqueous hydroxide are used in this procedure.

EXAMPLE 2

5 - (*p* - fluorobenzylideneamino) - salicylic acid

A mixture of 5 - aminosalicylic acid (0.005 m.) and *p* - fluorobenzaldehyde (0.005 m.) in ethanol (150 ml.) is heated, protected from moisture, for 5 hours, concentrated and cooled, and the 5 - (*p* - fluorobenzylidenamino) - salicylic acid collected.

A trace of *p* - toluene sulfonic acid may be used as a catalyst in the above reaction.

When *o*-, and *m* - fluorobenzaldehyde, *o*-, *m*- and *p* - chlorobenzaldehyde, *o*-, *m*-, and *p* - methylbenzaldehyde, *p* - dimethylamino - benzaldehyde, *o*, *m* and *p* - trifluoromethyl - benzaldehyde, *p* - acetamidobenzaldehyde, *o*-, *m*-, and *p* - methylthiobenzaldehyde, *p* - cyanobenzaldehyde, *m*- and *p* - benzyloxy - benzaldehyde, biphenylcarboxaldehyde, benzyl-benzaldehyde, *p* - phenoxybenzaldehyde, *p* - acetylbenzaldehyde, *p* - methylsulfonylbenz - aldehyde, dichlorobenzaldehyde, trichloro - benzaldehyde, 2,3,4,5 - tetramethylbenzaldehyde, or *p* - carbomethoxybenzaldehyde are used in place of *p* - fluorobenzaldehyde in the above procedure, the corresponding substituted benzalaminosalicylic acids are obtained.

When the 3 - chloro, 3 - methoxy, 3 - methyl, or 4 - fluoro analogues of 5 - aminosalicylic acid are used in place of 5 - aminosalicylic acid in the above example, the corresponding substituted salicylic acids are obtained.

EXAMPLE 3

5 - (*p* - fluorobenzylamino) - salicylic acid

A mixture of 5 - (*p* - fluorobenzylidene - amino) - salicylic acid (0.1 m.), ethanol (50 ml.) and 5% palladium on charcoal (0.5 g.) is reacted in a 40 p.s.i. hydrogen atmosphere at room temperature until 0.01 m. hydrogen has been absorbed. The mixture is filtered, the cake is washed well with ethanol and the filtrates are combined and concentrated *in vacuo* to 5 - (*p* - fluorobenzylamino) - salicylic acid.

The above reduction may be achieved using metal hydrides as the reducing agent.

The above product may also be obtained by direct *p* - fluorobenzylation of sodium (or potassium) 5 - amino - salicylate in ethanol containing anhydrous potassium carbonate.

When the substituted benzylideneamino compounds of Example 2 which are compatible with the reduction conditions are treated with hydrogen as above, the corresponding substituted 5 - benzylaminosalicylic acids are obtained.

EXAMPLE 4

5 - (*p* - fluoroanilinomethyl) - salicylic acid

A mixture of methyl 5 - chloromethyl - salicylate (0.01 m.), and *p* - fluoroaniline (0.01 m.) in methanol (25 ml.) containing anhydrous potassium carbonate is heated for 8 hours, cooled and filtered. The cake is washed well with fresh methanol, the combined filtrates concentrated *in vacuo*, the residue taken up in chloroform, dried and filtered, the chloroform removed *in vacuo*, and the residue chromatographed on a silica gel column using an ether-and-petroleum-ether system (v/v 10—100% ether) as eluant yielding methyl 5 - (*p* - fluoroanilinomethyl) salicylate. Hydrolysis of the ester yields 5 - (*p* - fluoroanilinomethyl) - salicylic acid.

When *o*-, and *m* - fluoroaniline, the tolu - idines, the anisidines, *o*-, *m*- and *p* - chloro-aniline, the trifluoromethylanilines, *o*-, *m* and *p* - nitroaniline, *o*-, *m*- and *p* - methyl - thioaniline, methyl *p* - aminobenzoate, the biphenylamines, *p* - benzylaniline, 4 - amino-phenyl ether, and 4 - benzyloxyaniline are used in place of *p* - fluoroaniline in the above reaction, the corresponding 5 - (anilino - methyl) - salicylate is obtained.

EXAMPLE 5A

3 - trifluoromethyl - 4 - nitroanisole

A stainless steel lined shaker is charged with 6 - nitro - *m* - anisic acid (0.1 m.) under a nitrogen atmosphere the system cooled in dry ice, sulfur tetrafluoride (0.5 m.) condensed into the tube, and the mixture then heated at 120°C. for 8 hours. After cooling, the tube is vented, the material taken up in chloroform, the chloroform mixture washed with dilute bicarbonate solution, the chloroform dried, filtered and concentrated *in vacuo*, and the residue chromatographed on a silica gel column using an ether-and-petroleum-ether system (v/v 0—80% ether) as eluant to yield 3 - trifluoromethyl - 4 - nitroanisole.

EXAMPLE 5B

4 - (*p* - fluorobenzamido) - 3 - trifluoro - methylanisole

A mixture of 4 - nitro - 3 - trifluoro - methylanisole (0.1 m.) and 5% palladium on charcoal catalyst (2 g.) in ethanol (500 ml.) is reacted with hydrogen (40 p.s.i.) at room temperature. When hydrogen uptake has stopped, the mixture is filtered, the ethanol removed *in vacuo*, anhydrous pyridine (300 ml.) added, and the resulting mixture treated with *p* - fluorobenzoyl chloride as in Example 1, 4 - (*p* - Fluorobenzamido) - 3 - trifluoro - methylanisole is obtained.

When the substituted benzoylhalides of Example 1 are used in place of *p* - fluoro - benzoyl chloride in Example 6, above, the correspondingly substituted benzamidoanisole is obtained.

When the free amino compound obtained above is benzylated with substituted benzylhalides as in Example 3, or using pyridine as the solvent base, the correspondingly substituted benzylamino anisole is obtained.

EXAMPLE 5C

p - (4 - fluorobenzamido) - m - trifluoro - methylphenol

A mixture of *p* - (4 - fluorobenzamido) - m - trifluoromethylanisole (5 g.) and pyridine hydrochloride (25 g.) under a dry nitrogen atmosphere is placed in an oil bath set at 230°, kept 10 minutes and cooled, and the mixture extracted with chloroform. The chloroform extracts are washed with water, dried, and concentrated *in vacuo*, and the residue chromatographed on a silica gel column using a methanol-and-methylene-chloride (v/v 0—50% methanol) system as eluant to yield *p* - (4 - fluorobenzamido) - *m* - trifluoromethylphenol.

When the other substituted benzamido and substituted benzylaminoanisoles of Example 5B, and 4 - amino - 3 - trifluoromethyl - anisole from Example 5B are reacted with pyridine hydrochloride as above, the corresponding phenols are obtained. Other standard procedures for demethylation may also be used.

EXAMPLE 5D

5 - (*p* - fluorobenzamido) - 4 - trifluoro - methylsalicylate acid

An intimately ground mixture of *p* - (4 - fluorobenzamido) - 3 - trifluoromethylphenol (5 g.) and anhydrous potassium carbonate (15 g.) is heated at 200°C. in a 1200—1400 p.s.i. carbon dioxide atmosphere for 8 hours. The mixture is cooled, added to water (300 ml.) stirred and filtered and the filtrate neutralized with dilute hydrochloric acid to yield 5 - (*p* - fluorobenzamido)- 4 - tri - fluoromethylsalicylic acid.

When the phenols of Example 5C are reacted with carbon dioxide as above, the correspondingly substituted salicylic acids are obtained.

EXAMPLE 6

5 - (*p* - fluorobenzylideneamino) - 4 - tri - fluoromethyl salicylic acid

When 5 - amino - 4 - trifluoromethyl - salicylic acid is reacted with *p* - fluorobenz - aldehyde as in Example 2, 5 - (*p* - fluoro - benzylideneamino) - 4 - trifluoromethyl salicylic acid is obtained.

When the benzaldehydes of Example 2 are used in place of *p* - fluorobenzaldehyde in the above case, the correspondingly substituted 5 - benzylideneaminosalicylic acid is obtained.

EXAMPLE 7

Methyl 5 (*p* - hydroxybenzylamino) - sali - cylate

When methyl 5 - (*p* - methoxybenzyl - amino) - salicylate is reacted with pyridine hydrochloride as in Example 5C, methyl 5 - (*p* - hydroxybenzylamino) - salicylate is obtained.

EXAMPLE 8

Methyl 5 - (*p* - mercaptobenzamido) - salicylate

When methyl 5 - (*p* - methylthiobenz - amido) - salicylate is reacted with pyridine hydrochloride as in Example 5C, methyl 5 - (*p* - mercaptobenzamido) - salicylate is obtained.

EXAMPLE 9

Methyl - 5 - (*p* - aminobenzamidosalicylate)

When methyl 5 - (*p* - nitrobenzamido) - salicylate in methanol is reacted with hydrogen as in Example 5B, methyl 5 - (*p* - amino-benzamidosalicylate is obtained.

When the nitro compounds of Examples 1 and 3 are used in the above process, the corresponding amino - substituted compounds are obtained.

EXAMPLE 10

5 - (*p* - methylsulfinylbenzamido) - salicylic acid

To 5 - (*p* - methylthiobenzamido) - salicylic acid (0.01 m.) in 1:1 methanol - acetone, ice-cooling and stirring, is added sodium metaperiodate (0.01 m.) in a minimum of water, and the reaction mixture stirred until precipitation of sodium iodate is completed. The mixture is filtered, the filtrate concentrated *in vacuo*, the residue taken up in chloroform, filtered and concentrated *in vacuo* to crude 5 - (*p* - methyl - sulfinylbenzamido) - salicylic acid.

When two equivalents of metaperiodate are used and the reaction carried out at c. 50°C., 5 - (*p* - methylsulfonylbenzamido) - salicylic acid is obtained.

When the methylmercapto compounds of Examples 2 and 3 are oxidized as above, the corresponding methylsulfinyl and methylsulfonyl analogues are obtained.

EXAMPLE 11

5 - (*p* - carboxybenzylaminosalicylic acid

To a solution of potassium hydroxide (0.05 m.) in water (100 ml.) is added 5 - (*p* - carbomethoxybenzylamino) - salicylic acid (0.01 m.) with stirring. The resultant mixture is heated gently for solution, stirred at room temperature for 5 hours and filtered. The pH of the filtrate adjusted with dilute hydrochloric acid and the 5 - (*p* - carboxybenzylamino) salicylic acid collected.

EXAMPLE 12

Methy 5 - (*p* - carbamoylbenzylamino) - salicylate

To a mixture of methyl 5 - (*p* - cyanobenzylamino) - salicylate (2 g.) in methylene chloride (25 ml.), is added manganese dioxide (12 g.) and the mixture is stirred for 70 hours at room temperature. The mixture is filtered, the cake washed well with warm methylene chloride, the filtrates concentrated *in vacuo* to a residue and the residue chromatographed on a silica gel column using a methanol-and-methylene-chloride system (v/v 0—8% methanol) as eluant to yield methyl 5 - (*p* - carbamoylbenzylamino) - salicylate.

The nitrile may also be converted to the amide using concentrated sulfuric acid in the cold.

EXAMPLE 13

Methyl 5 - (*p* - fluorobenzamido) - *o* - anisate

When methyl 5 - amino - *o* - anisate is reacted with *p* - fluorobenzoyl chloride as in Example 1, methyl 5 - (*p* - fluorobenzamido) - *o* - anisate is obtained.

When the other benzoylhalides of Example 1 are used in place of *p* - fluorobenzoyl chloride in the above reaction, the correspondingly substituted analogue is obtained.

When methyl 5 - amino - *o* - anisate is reacted with the aldehydes of Example 2 using the procedure of Example 2, the corresponding benzylideneaminoanisic acid derivatives are obtained.

When the benzylideneaminoanisic acid derivatives are reduced following the procedure of Example 3, the corresponding benzylaminoanisic acid derivatives are prepared.

EXAMPLE 14

Sodium 5 - (*p* - fluorobenzamido) - salicylate

To a solution of sodium hydroxide (0.001 m) in water (15 ml) is added 5 - (*p* - fluoro - benzamido) - salicylic acid (0.001 m) in ethanol, the mixture is stirred and gently heated for two hours, and the solvents removed *in vacuo* on a rotary evaporator to yield sodium 5 - (*p* - fluorobenzamido) - salicylate.

When one equivalent of potassium hydroxide or sodium carbonate is used in place of sodium hydroxide, the corresponding salt is prepared.

When two equivalents of the above bases are used in the above examples, the corresponding di - salt is obtained.

When 5 - (*p* - fluorobenzamido) - salicylic acid is replaced by the other salicylic acid compounds of this invention, the corresponding salt is obtained.

EXAMPLE 15A

m - Methoxymethylbenzoic acid

m - Carbomethoxybenzylbromide (0.02 m) is added to sodium methoxide (0.04 m) in methanol and the mixture heated gently for several hours. Water is added and the mixture is heated to boil away methanol, filtered and acidified with dilute hydrochloric acid to yield *m* - methoxymethylbenzoic acid.

When potassium methylthiolate is used in place of sodium methoxide in the above reaction, *m* - methylthiomethylbenzoic acid is obtained.

When *m* - carbomethoxybenzyl bromide is reacted with sodium benzylate or potassium benzylmercaptide, and the product hydrolysed as above, *m* - benzoyloxymethyl- and *m* - benzylthiomethylbenzoic acids are obtained.

EXAMPLE 15B

5 - (*m* - Methoxymethylbenzamido) - salicylic acid

m - Methoxymethylbenzoic acid (2 g) is added gradually to stirred thionyl chloride (20 ml), heated gently until reaction ceases, and the excess of thionyl chloride removed *in vacuo*. Anhydrous benzene (30 ml.) is added, and then removed *in vacuo* to get rid of traces of thionyl chloride. The residual *m*-methoxymethylbenzoyl chloride is used without purification in the reaction with 5 - amino-

salicylic acid, by the procedure of Example 1, to yield 5 - (*m* - methoxymethylbenz - amido) - salicylic acid.

When *m* - methylthiomethylbenzoic acid, *m* - benzyloxymethylbenzoic acid, and *m* - benzylthiomethylbenzoic acid of Example 18 are used in place of *m* - methoxymethylben - zoic acid, above 5 - (*m* - methylthiomethyl - benzamido) salicylic acid, 5 - (*m* - benzyl - oxymethylbenzamido) - salicylic acid, and 5 - (*m* - benzylthiomethylbenzamido) - salicylic acid are obtained, respectively.

Phosphorus pentachloride and phosphorus oxychloride may be used in place of thionyl chloride in the above reaction.

EXAMPLE 16

Methyl 5 - (*m* - hydroxymethylbenzamido) - salicylate

A mixture of methyl 5 - (*m* - benzyl - oxymethylbenzamido) - salicylate (0.01 m.), methanol (100 ml.) and 5% palladium on charcoal (0.5 g.) is subjected to a 40 p.s.i. hydrogen atmosphere at room temperature, removed when 0.01 m. hydrogen has been absorbed, filtered and concentrated *in vacuo*. The residue is chromatographed on a silica gel column using an ether-and-petroleum-ether system (v/v 5—90% ether) as eluant to yield methyl 5 - (*m* - hydroxymethyl - benzamido) - salicylate.

When methyl 5 - (*m* - benzylthiomethyl - benzamido) - salicylate is reduced as above, methyl 5 - (*m* - mercaptomethylbenzamido) - salicylate is obtained.

EXAMPLE 17

Methyl 5 - (*p* - aminomethylbenzylamino) - salicylate dihydrochloride

Methyl 5 - (*p* - cyanobenzylamino) - salicylate (0.01 m.) in acetic acid (100 ml.) is reduced at room temperature under a 40 p.s.i. hydrogen atmosphere, using 0.5 g. platinum oxide as a catalyst. When the theo-retical amount of hydrogen is consumed, the mixture is filtered, the solvent removed *in vacuo*, the residue taken up in chloro - form - ether and filtered, anhydrous ethereal hydrogen chloride added and the methyl 5 - (*p* - aminomethylbenzylamino) - salicylate di-hydrochloride collected.

EXAMPLE 18

Methyl 5 - (*p* - dimethylaminomethylbenzyl-amino) - salicylate

A mixture of methyl 5 - (*p* - amino - methylbenzylamino) salicylate (0.008 m.), 37% formaldehyde (6 ml.), dried 1,2 - di - methoxyethane (120 ml.), glacial acetic acid (50 ml.) and Raney nickel (2 tsp.) is treated with hydrogen (40 p.s.i.) at room tempera-ture. When uptake is completed, the mixture is filtered, the cake washed well with fresh dimethoxy ethane, and the combined filtrates distributed between chloroform and dilute aqueous sodium bicarbonate solution. The chloroform layer is dried and concentrated, and the residue chromatographed on a silica gel column using a methanol-and-methylene-chloride system (v/v 0—90% methanol) as eluant to yield methyl 5 - (*p* - dimethylamino-methylbenzylamino) - salicylate.

EXAMPLE 19

Methyl 2 - carboxy - 4 - (*p* - fluoro - benzamido) - phenyl carbonate

To a mixture of 5 - (*p* - fluorobenz - amido) - salicylic acid (0.01 m.), dimethyl - aniline (0.20 m.) and benzene (30 ml.) is added methyl chloroformate (0.01 m.) over one hour with constant shaking and cooling. When the odor of the chlorocarbonate is absent, hydrochloric acid (1*N*, 100 ml.) is added and the mixture filtered. The benzene layer is separated, dried and filtered, and the benzene removed *in vacuo* to yield methyl 2 - carboxy - 4 - (*p* - fluorobenzamido) - phenyl carbonate.

EXAMPLE 20

N - (3 - carboxy - 4 - hydroxybenzal) - *p* - fluoroaniline

When 5 - formylsalicylic acid (0.005 m.) and *p* - fluoroaniline are reacted as per Example 2, N - (3 - carboxy - 4 - hydroxy - benzal) - *p* - fluoronaniline is obtained.

When other substituted aniline compounds are used in place of *p* - fluoroaniline in the above procedure, the corresponding substituted phenyliminomethylsalicylic acids are obtained.

EXAMPLE 21

Methyl 5 - (*p* - fluorobenzylamino) - salicylate

To a mixture of 5 - (*p* - fluorobenzyl - amino) - salicylic acid (0.015 m.) and absolute methanol (50 ml.), is added slowly, with stirring, concentrated sulfuric acid (2.0 ml.). The mixture is then heated gently for 18 hours. Excess of methanol is removed by evaporation *in vacuo*, the residue is parti-tioned between chloroform and water, and the chloroform layer washed with dilute sodium bicarbonate solution and water, dried, filtered and concentrated to yield methyl 5 - (*p* - fluorobenzylamino) - salicylate.

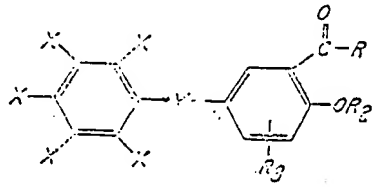
When the 5 - (*p* - fluorobenzylamino) - salicylic acid of the above procedure is re-placed by any of the other salicylic acid compounds of this invention, the correspond-ing methyl ester is prepared.

When methanol in the above procedure is replaced by other appropriate alcohols such as ethanol, propanol, isopropanol, butanol, iso-butanol, 2 - methoxyethanol or 2 - ethoxy - ethanol, the corresponding ester is prepared.

Diazo compounds, such as diazomethane, may also be used to prepare the correspond-ing ester. In some cases this is preferred.

WHAT WE CLAIM IS:—

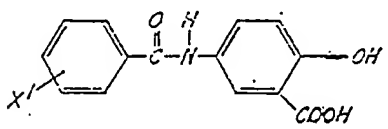
1. A compound of the formula:



in which R is hydroxy, amino, alkoxy, alkylamino, dialkylamino, dialkylaminoalkyl - amino, dialkylaminoalkoxy, hydroxyalkoxy, polyhydroxyalkoxy, alkoxyalkoxy, phenyl - alkoxy, phenoxy, substituted phenoxy, (C_{1-6} alkanoylamino)alkoxy, hydrazino, anilino, morpholino, N - piperidino, pyrrolidino or hydroxyalkylamino radical or an N - attached radical derived from an amino acid; R_2 is a hydrogen atom or an acyl, alkyl or alkoxycarbonyl radical; R_3 is a hydrogen or halogen atom or a haloalkyl, alkyl, cycloalkyl or alkoxy radical; each X, which may be the same as or different from the others, is a hydrogen or halogen atom or an alkyl, hydroxy, alkoxy, acyloxy, haloalkyl, nitro, amino, alkylamino, dialkylamino, acylamino, mercapto, alkylthio, alkylsulfinyl, alkylsulfonyl, sulfamoyl, aminosulfinyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, hydroxyalkyl, alkoxyalkyl, mercaptoalkyl, alkylthioalkyl, cyano, carboxy, alkoxycarbonyl, carbamoyl, aryl, aralkyl, salicyl, aryloxy, or aralkoxy radical; and Y is a methyleneimino ($-CH_2NH-$), iminomethyl ($-NHCH_2-$), methinenitrilo ($-CH=N-$), nitrilomethine ($-N=CH-$) or carbonylimino ($-\overset{O}{\overset{\|}{C}}NH-$), radical, all alkyl and alkoxy radicals and residues mentioned in the definitions of R, R_2, R_3 and X containing not more than five carbon atoms unless forming part of an alkoxycarbonyl radical.

2. A compound as claimed in claim 1 in which R is a hydroxy or amino radical; R_2 is a hydrogen atom or an alkyl radical; R_3 is a hydrogen or halogen atom or an alkyl radical; and X is a hydrogen or halogen atom or an alkoxy, haloalkyl or dialkylamino radical.

3. A compound of the formula:



in which X′ is a halogen atom.

4. A non-toxic pharmaceutically acceptable salt of a compound as claimed in claim 1 or 2 in which R is a hydroxy radical.

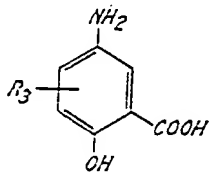
5. A non-toxic pharmaceutically acceptable salt of a compound as claimed in claim 3.

6. 5 - (*p* - Fluorobenzylamino) - salicylic acid.

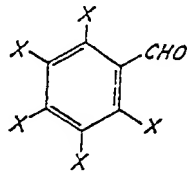
7. 5 - (*p* - Fluorobenzamido) - salicylic acid.

8. 5 - (*p* - Fluorophenyliminomethyl) - salicylic acid.

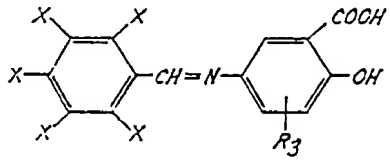
9. The process that comprises reacting an aminosalicylic acid compound of general formula:



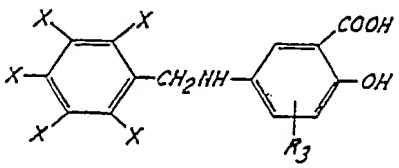
with a benzaldehyde compound of general formula:



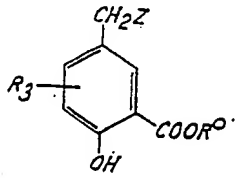
where R_3 and X are as defined in claim 1, to produce a compound of general formula:



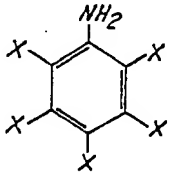
10. A process as claimed in claim 9, including the further step of reducing the product a compound of general formula:



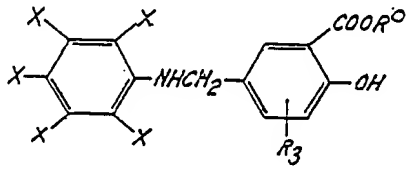
11. The process that comprises reacting a halomethyl salicylic acid compound of general formula:



with an aniline compound of general formula:

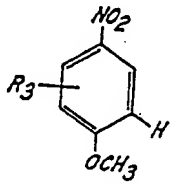


where R_3 and X are as defined in claim 1, R° is a hydrogen atom or a methyl radical and Z is a halogen atom to produce a compound of general formula:

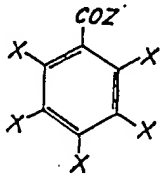


and, when R° is a methyl radical, optionally hydrolysing the product to give the corresponding free acid, in which R° is a hydrogen atom.

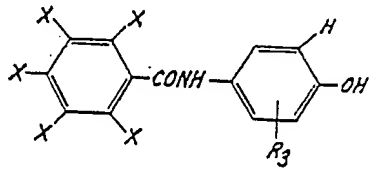
12. The process that comprises reducing a 4 - nitro - anisole compound of general formula:



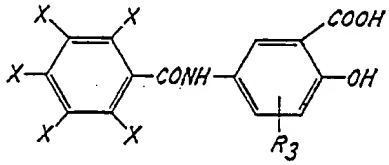
to the corresponding 4 - amino - anisole compound, reacting the latter with a benzoyl halide compound of general formula:



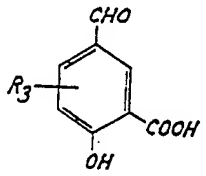
where R_3 and X are as defined in claim 1 and Z is a halogen atom, to produce a benzamidoanisole, demethylating the latter to produce a benzamidophenol compound of formula:



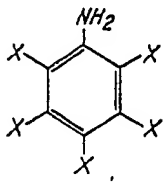
and carboxylating this to produce a compound of general formula:



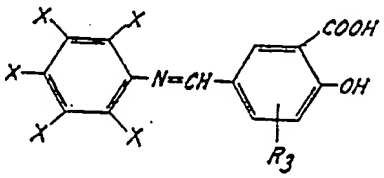
13. The process that comprises reacting a 5 - formyl salicylic acid compound of general formula:



with an aniline compound of general formula:



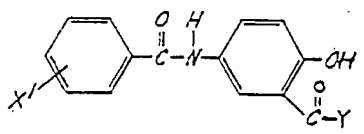
where R_3 and X are as defined in claim 1 to produce a compound of general formula:



14. A process as claimed in any one of claims 9—13, including the further step of esterifying, amidating or forming a salt with the COOH group and/or alkylating the OH group.

15. A process that produces a compound as claimed in claim 1, substantially as hereinbefore described in any one of the foregoing examples.

16. The preparation of a compound as claimed in claim 3 by hydrolysing an ester of the formula:



where X′ is halogen and Y is lower alkoxy.

17. A compound as claimed in claim 1 when prepared by a process as claimed in any one of claims 9—15 or an obvious chemical equivalent of such a process.

18. Each and every compound as claimed in claim 1 hereinbefore individually specified, with the exception of those claimed in claims 6, 7 and 8.

19. A pharmaceutical composition comprising at least one compound as claimed in claim 1, 2 or 4, and a pharmaceutically acceptable carrier.

20. A pharmaceutical composition comprising at least one compound as claimed in any one of claims 1—8, 17 and 18 as an active ingredient, together with a pharmaceutically acceptable diluent, carrier or coating.

21. A composition as claimed in claim 19, in the form of a tablet, capsule, lozenge, troche, powder, gel, suppository, lotion, syrup or liquid suspension.

22. A composition as claimed in claim 20, in the form of a tablet, capsule, lozenge, troche, powder, gel, suppository, lotion, syrup, elixir, liquid suspension, pill, cream, ointment or buffered injectable solution.

23. A method of treating inflammation in non-human animals which comprises administering to a host animal 1 mg to 100 mg per kg body weight per day of a compound as claimed in any one of claims 1—8, 17 and 18.

For the Applicants,
D. YOUNG & CO.,
Chartered Patent Agents,
9 & 10 Staple Inn,
London WC1V 7RD.

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